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56 References cited:

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GB-A- 516 289  
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Columbus, Ohio, US, L.J.D. ZANEVELD et al.:  
"Synthetic enzyme inhibitors as antifertility  
agents"

UNLISTED DRUGS, vol. 24, April 1972, page 57  
Chatham, New Jersey, US

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G. WAGNER et al.: "Synthese antiproteolytisch  
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Courier Press, Leamington Spa, England:

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## Description

This invention relates to intrauterine devices and more particularly to an improved intrauterine device wherein there is a cavity provided in at least a portion of the intrauterine device and a concentrated fluid solution of a drug providing antifibrinolytic, antifertility and antiproteolytic effect is provided within the cavity.

Many forms and configurations of intrauterine devices designed to prevent conception in the female have heretofore been utilized. Such devices have been provided in a variety of shapes, such as the "T" device shown in U.S. Patent 3,533,406, the Loop, such as shown in Patent 3,200,815, a "Y" configuration, generally termed a "Ypsilon" configuration, a ring or modified ring such as the Ota ring, and many modifications thereto, including flat, leaf-like members between various segments of the intrauterine device. Such intrauterine devices which were not provided with any medications associated therewith depended upon their presence in the uterus to prevent conception.

Further, other intrauterine devices (IUDs) have incorporated a controlled release rate medication or drug therein to further aid the anticonceptive action thereof. Such medicated IUDs have generally employed copper or progesterone as the contraceptive or antifertility agent. However, it has been found that copper-releasing intrauterine devices, as well as non-medicated intrauterine devices still resulted in pain and cramping to the wearer, as well as metrorrhagia and menorrhagia. Consequently, the excessive uterine hemorrhage, with or without pain, continues to be a leading cause for this type of intrauterine device removal. The progesterone-releasing intrauterine devices are associated with significantly less bleeding than other devices but they appear to be associated with a serious complication apparently produced by the release of progesterone. This complication is ectopic pregnancy.

Nevertheless, the general convenience and safety of intrauterine devices continues to give hope that the IUD may one day provide an ideal method for worldwide population control, since it has been found, statistically, that intrauterine devices can provide effective contraception in a 98—99% range of effectivity, they do not require conscious effort, are less subject to human failings than any other type of contraceptive, their antifertility effect is completely reversible, they have minimal, if any systemic effect, and their effect is confined essentially to the uterus. However, it is believed that even greater antifertility effect can be achieved by utilizing other anticonceptive agents with an IUD, which agents do not have the serious detrimental side effects noted above.

Consequently, there has been a need for improved medicate intrauterine devices providing greater antifertility effect and in which the side effects of pain, metrorrhagia and/or menorrhagi are reduced or eliminated, and which are not associated with other serious side effects such as ectopic pregnancy.

While the inflammatory response of the endometrium to intrauterine devices has heretofore been known, I have discovered that the chronic response of the endometrium to long-term intrauterine device exposure is more a humoral type of reaction (accompanied by increase vascular permeability with edema and interstitial hemorrhage) than the immunologic or cellular type of response (accompanied by infiltration of immune complexes or of leukocytes, such as plasma cells or neutrophils). However, I have found that there are defects in small endometrial vessels which suggest damage caused by mechanical distortion of the uterine tissues. The defects generally lack hemostatic plugs of platelets and/or fibrin. Further, there is evidence that fibrinolysis is activated in the uterus in response to the presence of an intrauterine device. This activation could result in blockage of normal hemostatic reaction at several levels in the coagulation system. Further, it may initiate, aid, or aggravate humoral inflammation by any one or all of the following mechanisms:

1. Activation of the complement system and histamine release;
2. Activation of prekallikrein; and
3. Release of fibrin degradation fragments.

Histamine can cause vascular dilation and increase vascular permeability. Kallikrein (activated prekallikrein) releases bradykinin which can have an effect similar to histamine and may also cause cramping and pain. Fibrin degradation fragments may enhance the vascular effects of histamine and bradykinin. Combined with distortion of the endometrium caused by myometrial contractility around the relatively inelastic or unyielding IUD, which may also be associated with increased prostaglandin synthesis and release, it may be predicted that excessive bleeding from leaky or broken vessels will occur. For these reasons, incorporation into medicated IUD devices of potent inhibitors of plasminogen activation and plasmin activity (fibrinolytic activity for the purposes of intrauterine release over an extended time period can provide an alleviation of the aforesaid undesired effects.

It has also heretofore been found that IUD associated uterine hemorrhage can be alleviated by the systemic (oral) intake of the fibrinolytic inhibitors epsilon aminocaproic acid (EACA) and tranexamic acid. I have also demonstrated that an EACA loaded IUD inserted into the uterus of rhesus monkeys provides an ameliorative effective by such medicated devices on fibrinolytic activity in these animals. However, neither EACA nor tranexamic acid would appear to be satisfactory agents for long-time intrauterine medication. First, they are not highly potent anti-firinolytic agents and would have to be delivered at a rather high rate into the uterine cavity. Thus, a drug loaded IUD would become exhausted of its medication in a short period of time, or would require an unacceptably large size of device. In

addition, EACA and tranexamic acid are small molecules which are highly diffusible and water soluble. Therefore, intrauterine release thereof from a medicated intrauterine device at a steady, constant rate is difficult to control and effective concentration inside the uterus difficult to maintain. Consequently, inhibitor concentrations of either EACA and tranexamic acid of between  $1 \times 10^{-3}$  and  $1 \times 10^{-4}$  Mol/liter, which is the concentration of these drugs required to be effective, respectively, over a prolonged period of time is generally not achievable considering the amount of medication which is feasible to load into an IUD and considering the diffusion and solubility properties of these compounds and the rate of water turnover inside the uterus.

While there heretofore has been some indication that certain compounds used for treatment of protozoal, bacterial and fungal infections may have anti-fibrinolytic properties, there has not heretofore been any indication of anti-fertility action of these compounds added to an intrauterine device. These compounds may be generally defined as the aromatic amidines, and in particular, the aromatic diamidines. However, heretofore, it has not been specifically recognized that their anti-fibrinolytic action inside the uterus can alleviate the metrorrhagia and menorrhagia. Further, even though such metrorrhagia and menorrhagia may be alleviated, the pain and cramps associated with intrauterine devices could still remain a major drawback to effective extensive use of medicated intrauterine devices as a population control technique.

Additionally, in many prior art IUDs, expulsion thereof is a somewhat frequent occurrence. Such undesired expulsion is another drawback of prior art IUDs.

In addition to the above-mentioned types of intrauterine devices, there is also heretofore been provided intrauterine devices in which all or a part of the device is hollow and thus the device has walls defining the cavity. Such a device is shown, for example, in Patent 3,896,819 and other types of such devices are shown, for example, in Patents 3,710,795 in which the cavity is filled with a solid matrix, and other prior art patents. Similarly, there have heretofore been proposed inflatable intrauterine devices in which the walls of the intrauterine device are flexible and it is inserted into the uterus in uninflated condition and subsequently expanded.

However, in none of the prior art devices has there heretofore been provided a drug releasable at a controlled rate over an extended period of time which drug provides not only an antiproteolytic action but an enhanced contraceptive action. Accordingly, there has long been a need for an intrauterine device which can provide the above desiderata.

Additionally, in many prior art IUDs, expulsion thereof is a somewhat frequent occurrence. Such undesired expulsion is another drawback of prior art IUDs.

Consequently, there has long been a need for a medicated intrauterine device which not only enhances the antifertility action of the IUD but also provides reduction or elimination of metrorrhagia or menorrhagia for an extended period of time, as well as decreasing the pain and cramps associated with wearing an intrauterine device, as well as decreasing the tendency of expulsion thereof.

Contraceptive effects of certain guanidine and amidine compounds and groups of compounds are disclosed in:—

"CHEMICAL ABSTRACTS", Vol. 74, abstract No. 74827z.

"UNLISTED DRUGS", Vol. 24, page 57, abstract a and

"UNLISTED DRUGS", Vol. 24, page 53, abstract c.

"DIE PHARMAZIE", Vol. 25, pages 551—554 and Vol. 28, pages 293—6 disclose antiproteolytic properties of guanidine and amidine derivatives.

DE—A—2 247 949 discloses devices for controllably releasing drugs, for example an intrauterine device for releasing contraceptive agents.

It is an object of the present invention to provide an improved intrauterine device.

According to the present invention I provide a medicated intrauterine device of the type insertable in the uterus and having a surface adapted to contact the uterus and said device including at least one wall defining a fluid-receiving cavity for a medicament said wall serving to control the rate of release of the medicament characterised in that the medicament is a drug comprising an amidine and/or a guanidine or an ester or salt thereof which is capable of exhibiting an anti-proteolytic, an anti-fibrinolytic and anti-conceptive effect when released at said controlled rate.

The drug may also provide a reversible anti-conceptive effect.

Preferably, the drug is:—

- (a) an amidine;
- (b) a mixture of an amidine and a guanidine;
- (c) a mixture of more than one amidine and a guanidine;
- (d) a mixture of an amidine and more than one guanidine;
- (e) a mixture of more than one amidine and more than one guanidine;
- (f) a guanidine; and
- (g) a mixture of more than one guanidine.

The anti-proteolytic action and, in particular, the anti-fibrinolytic action of the aromatic monoamidines, aromatic diamidines and non-aromatic diamidines can provide a reduction in metrorrhagia and menorrhagia because of the particular characteristics associated with the reaction of

the endometrium and/or the fluid of the uterus to the presence of an intrauterine device. Further, it is believed that inhibition of other proteolytic systems in the endometrium and/or muscle wall of the uterus can reduce and/or eliminate the pain and cramps associated with wearing an intrauterine device. Further, it is believed that inhibition of other proteolytic systems in the endometrium and/or muscle wall of the uterus can reduce and/or eliminate the pain and cramps associated with wearing an intrauterine device, as well as minimizing the risk of expulsion thereof. The amidines and, in particular, the aromatic monoamidines, aromatic diamidines, and non-aromatic diamidines, have been found to possess the desired properties, due to the anti-fibrinolytic and other antiproteolytic effect thereof, to reduce or eliminate metrorrhagia and/or menorrhagia.

Additionally, I have discovered that there is a surprising and unexpected result in utilization of aromatic diamidines with intrauterine devices in that they enhance the antifertility effect the IUD. That is, they may cause a greater contraceptive effect than has heretofore been obtainable with prior art IUDs of either the plain or medicated type. This unexpected result, it is believed, is achieved by the mechanism of the aromatic diamidine acting upon the fertilized egg or the blastocyst (preimplantation embryo) to cause it to degenerate. The aromatic diamidine could, in addition, act on the sperm to either kill or render them ineffective in fertilization.

I have also discovered that the guanidines, in addition to the amidines, have such properties and, it is believed, may have even more potent effects.

Thus, I have discovered that there is a surprising and unexpected result in utilization of guanidines with intrauterine devices in that they may decrease IUD induced uterine bleeding and enhance the antifertility effect of the IUD by providing an anti-proteolytic and, particularly, an anti-fibrinolytic action in the uterus. Each treated IUD, therefore, may, additionally, cause a greater contraceptive effect than has heretofore been obtainable with the above-mentioned prior art IUDs of either the plain or medicated type. This unexpected result, it is believed, is achieved by the mechanism of the guanidine acting upon the fertilized egg or the blastocyst (preimplantation embryo) to cause it to degenerate. The guanidine could, in addition, act on the sperm to either kill or render them ineffective in fertilization.

Further, it is believed, that certain anti-proteolytic action of the aromatic diamidines and guanidines could reduce or eliminate the pain and cramps often associated with wearing an IUD.

In the present invention, the IUD is in the form of a uterus insertable body member having first walls defining a cavity therein. The cavity may extend throughout the IUD or only for a portion thereof. Further, the walls defining the cavity may be semi rigid or flexible. In the flexible walled IUD, the IUD may be inserted into the uterus in an uninflated condition and then subsequently expanded by filling with the solution containing the required concentration of the drug. The walls defining the cavity are permeable to the drug.

The drug, which may be one or more drugs selected from the class consisting of aromatic monoamidines, aromatic diamidines, non-aromatic diamidines, aromatic monoguanidines, aromatic diguanidines, non-aromatic monoguanidines and non-aromatic diguanidines, or a mixture of one, or more guanidines with one or more amidines, is provided within the cavity. The permeability of the walls defining the cavity allows a predetermined, controlled release rate of the drug to the uterus. The term "drug" as utilized herein refers to either a single one of the above-mentioned amidines or guanidines, or a mixture of more than one guanidines with one or more of the amidines. In addition, if desired, a coating of the drug may also be provided on some or all of the external surface of the body member. The coating may be covalently bonded to the surface of the body member and consists of a non-biodegradable monomer, dimer, oligomer, or cross-linked polymer of the drug. Such embodiment provides a prolonged surface effect for reducing deleterious effects on the uterine wall, as well as provides the desired prolonged release of the drug from the body member. The bleeding of the endometrium in contact with the intrauterine device is at the surface of the endometrium. The inhibition of plasminogen activator and plasmin by solid phase enzyme inhibitors such as the surface linked drugs described in this paragraph constantly during the wearing of the intrauterine device could lead to a lessening of the bleeding at the interface between the endometrium and the intrauterine device.

In another embodiment of the present invention, the surface of the body member of any one of the above-defined embodiments may be partially covered by metallic copper to provide additional anti-conceptive action for the device.

The drug may be utilized either in its base form, or as certain esters such as isethionate, or as certain salts, such as hydrochloride or phosphate, depending upon the degree of solubility desired in the uterine fluid for control of release rate and tissue uptake of the drug, as well as enhancing the effectiveness of the particular compound employed.

Reference is now made to the accompanying drawing wherein similar reference characters refer to similar elements throughout and in which:

Figure 1 and 1A illustrate embodiments of an intrauterine device useful in the practice of the invention;

Figure 2 illustrates another embodiment of an intrauterine device useful in the practice of the present invention;

Figure 3 illustrates another embodiment of an intrauterine device useful in the practice of the present invention;

Figure 4 illustrates another embodiment of an intrauterine device useful in the practice of the present invention; and

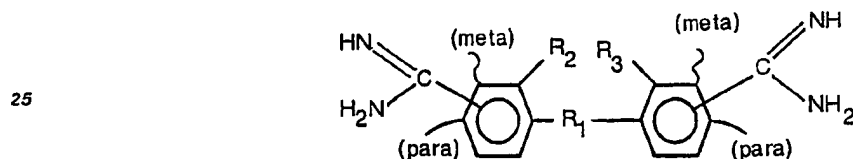
Figure 5 illustrates another embodiment of an intrauterine device useful in the practice of the present invention.

As noted above, the present invention is a medicated intrauterine device wherein a preselected drug is provided in a concentrated solution in the cavity of the body member of an IUD. As utilised herein and in the appended claims, the term "drug" refers to one or a mixture of more than one of a preselected compound. The preselected compounds of the present invention are aromatic amidines and in particular the aromatic monoamidines, aromatic diamidines and non-aromatic diamidines, and the guanidines and in particular the aromatic monoguanidines, the aromatic diguanidines, and non-aromatic monoguanidines, and the non-aromatic diguanidines.

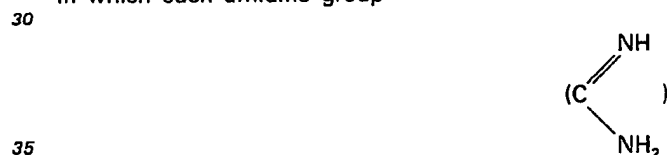
The aromatic amidines may be an aromatic monoamidine of the general formula:



wherein: R is a carbon chain or an aromatic group or an aromatic group with or without other elements, or, as preferred for utilization in the invention herein, an aromatic diamidine of the general formula:



in which each amidine group



may be substituted in either a meta or para position with respect to R<sub>1</sub>, wherein:

R<sub>1</sub> is generally a carbon chain with or without either bonds to the benzene rings;  
R<sub>2</sub> and R<sub>3</sub> can be hydrogen, chlorine, bromine, iodine, hydroxyl group, alkyl, or other group; and



represents the benzene ring.

The aromatic guanidines may be an aromatic monoguanidine of the general formula:



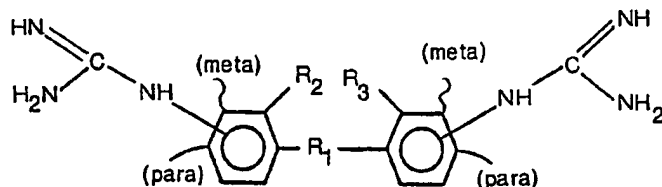
wherein:

R is a carbon chain with or without other elements (such as hydrogen, nitrogen, oxygen, sulfur, etc.); an aromatic group (such as benzene) with or without additional carbons, carbon chains, and other elements; a cyclic non-aromatic group (such as cyclohexane) with or without additional carbons, carbon chains, and other elements; or any of the above in combination; and

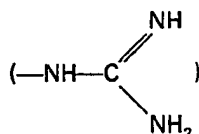


represents the benzene ring.

As preferred for utilization in the invention herein, there may be utilized an aromatic diguanidine of the general formula:



in which each guanidine group:



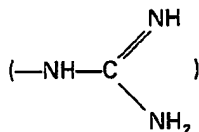
may be substituted in either a meta or para position with respect to  $R_1$ , and wherein:  
 $R_1$  is generally a hydrocarbon chain with or without ether or ester bonds to the benzene rings;  
 $R_2$  and  $R_3$  can be hydrogen, chlorine, bromine, iodine, hydroxyl group, alkyl, or other group; and



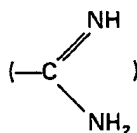
represents the benzene ring.

Table I below lists particular aromatic diamidines useful in the practice of the present invention.

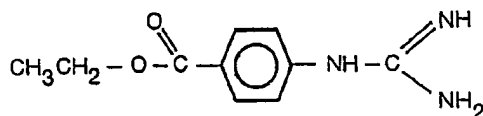
It is understood that the series of examples of aromatic diamidines in Table I, below will also exemplify the aromatic diguanidines in every respect except that for the latter class of compounds guanidino groups:



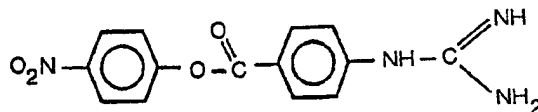
are substituted for amidino groups:



Two examples of aromatic monoguanidines are the following

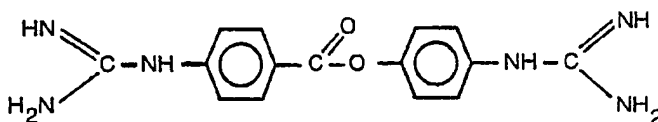


ether-p-guanidinobenzoate and



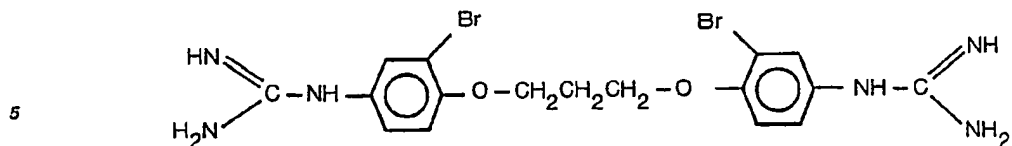
p-nitrophenyl-p'-guanidinobenzoate (commonly named NPGb).

Two examples of aromatic diguanidines are the following:



P-guanidinophenyl-p' guanidinobenzoate and

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1,3-bis (2-bromo-4-guanidinophenoxy) propane.

10 [This last compound is analogous to dibromopropamidide (Table I) except that it is a diguanidine rather than a diamidine by virtue of the two guanidino groups:

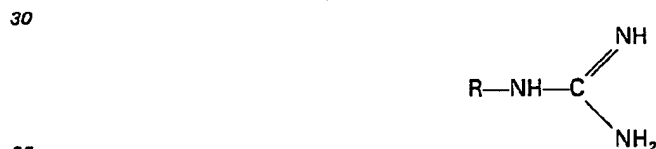


at both extremities of the molecule in place of the two amidino groups:



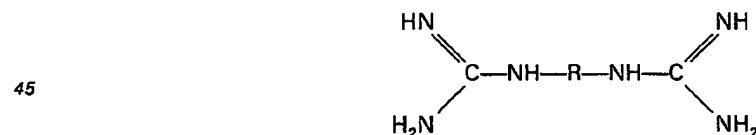
25 This diguanidine is assigned a chemical name in this application rather than a common or trivial name (such as "dibromopropaguanidine") because the compound and its analogs are not in common use and have not been previously given common names in the scientific literature.].

The non-aromatic guanidines may be a non-aromatic monoguanidine of the general formula:



wherein R may represent a carbon chain with or without other elements (such as hydrogen, nitrogen, oxygen, sulfur, etc.); a cyclic non-aromatic group (such as cyclohexane) with or without additional carbons, carbon chains, and other elements; or any of the above in combination.

40 As preferred for utilization in the invention herein, there may be utilized a non-aromatic diguanidine of the general formula:



R may represent a carbon chain with or without other elements (such as hydrogen, nitrogen, oxygen, sulfur, etc.); a cyclic aromatic group (such as cyclohexane) with or without additional carbons, carbon chains, and other elements; or any of the above in combination

An example of a non-aromatic monoguanidine is the following:

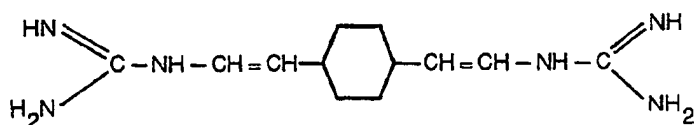


60 guanidinocyclohexane.

An example of a non-aromatic diguanidine is the following:

65

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1,4-di(2-guanidinovinyl)cyclohexane.  
In the above,



represents cyclohexane.

TABLE I  
AROMATIC DIAMIDINES

Drug Name	R <sub>1</sub> Carbon Chain	R <sub>2</sub>	R <sub>3</sub>	Relative Potency
Dibromopropamidine	C <sub>3</sub> H <sub>6</sub>	Br	Br	1.0
Phenamidine	—	H	H	0.2
Octamidine	C <sub>8</sub> H <sub>16</sub>	H	H	2.6
m-Pentamidine	C <sub>5</sub> H <sub>10</sub>	H	H	0.6
Hexamidine	C <sub>6</sub> H <sub>12</sub>	H	H	1.6
Dichlorohexamidine	C <sub>6</sub> H <sub>12</sub>	Cl	Cl	1.9
Pentamidine	C <sub>5</sub> H <sub>10</sub>	H	H	2.4
Monoiodohexamidine	C <sub>6</sub> H <sub>12</sub>	I	H	4.4
Dibromopentamidine	C <sub>5</sub> H <sub>10</sub>	Br	Br	3.6
Propamidine	C <sub>3</sub> H <sub>6</sub>	H	H	1.2
Heptamidine	C <sub>7</sub> H <sub>14</sub>	H	H	1.9
Diiodopentamidine	C <sub>5</sub> H <sub>10</sub>	I	I	6.8
Diiodohexamidine	C <sub>6</sub> H <sub>12</sub>	I	I	7.5
Butamidine	C <sub>4</sub> H <sub>8</sub>	H	H	
Monochloropropamidine	C <sub>3</sub> H <sub>6</sub>	Cl	H	
Monochlorobutamidine	C <sub>4</sub> H <sub>8</sub>	Cl	H	
Monochloropentamidine	C <sub>5</sub> H <sub>10</sub>	Cl	H	
Monochlorohexamidine	C <sub>6</sub> H <sub>12</sub>	Cl	H	
Monochloroheptamidine	C <sub>7</sub> H <sub>14</sub>	Cl	H	
Monochlorooctamidine	C <sub>8</sub> H <sub>16</sub>	Cl	H	
Monochlorononamidine	C <sub>9</sub> H <sub>18</sub>	Cl	H	
Monobromopropamidine	C <sub>3</sub> H <sub>6</sub>	Br	H	



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TABLE 1 (continued)

AROMATIC DIAMIDINES

5	Drug Name	R <sub>1</sub> Carbon Chain	R <sub>2</sub>	R <sub>3</sub>	Relative Potency
	Monobromofutamidine	C <sub>4</sub> H <sub>8</sub>	Br	H	
10	Monobromopentamidine	C <sub>5</sub> H <sub>10</sub>	Br	H	
	Monobromohexamidine	C <sub>6</sub> H <sub>12</sub>	Br	H	
	Monobromoheptamidine	C <sub>7</sub> H <sub>14</sub>	Br	H	
15	Monobromooctamidine	C <sub>8</sub> H <sub>16</sub>	Br	H	
	Monobromononamidine	C <sub>9</sub> H <sub>18</sub>	Br	H	
20	Moniodopropamidine	C <sub>3</sub> H <sub>6</sub>	I	H	
	Moniodobutamidine	C <sub>4</sub> H <sub>8</sub>	I	H	
	Moniodopentamidine	C <sub>5</sub> H <sub>10</sub>	I	H	
25	Moniodohexamidine	C <sub>6</sub> H <sub>12</sub>	I	H	
	Moniodoheptamidine	C <sub>7</sub> H <sub>14</sub>	I	H	
30	Moniodooctamidine	C <sub>8</sub> H <sub>16</sub>	I	H	
	Moniodononamidine	C <sub>9</sub> H <sub>18</sub>	I	H	
	Dichloropropamidine	C <sub>3</sub> H <sub>6</sub>	Cl	Cl	
35	Dichlorobutamidine	C <sub>4</sub> H <sub>8</sub>	Cl	Cl	
	Dichloropentamidine	C <sub>5</sub> H <sub>10</sub>	Cl	Cl	
40	Dichlorohexamidine	C <sub>6</sub> H <sub>12</sub>	Cl	Cl	
	Dichloroheptamidine	C <sub>7</sub> H <sub>14</sub>	Cl	Cl	
	Dichlorooctamidine	C <sub>8</sub> H <sub>16</sub>	Cl	Cl	
45	Dichlorononamidine	C <sub>9</sub> H <sub>18</sub>	Cl	Cl	
	Dibromopropamidine (already listed)	C <sub>3</sub> H <sub>6</sub>	Br	Br	
50	Dibromobutamidine	C <sub>4</sub> H <sub>8</sub>	Br	Br	
	Dibromopentamidine	C <sub>5</sub> H <sub>10</sub>	Br	Br	
55	Dibromohexamidine	C <sub>6</sub> H <sub>12</sub>	Br	Br	
	Dibromoheptamidine	C <sub>7</sub> H <sub>14</sub>	Br	Br	
	Dibromooctamidine	C <sub>8</sub> H <sub>16</sub>	Br	Br	
60	Dibromononamidine	C <sub>9</sub> H <sub>18</sub>	Br	Br	
	Diiodopropamidine	C <sub>3</sub> H <sub>6</sub>	I	I	
65	Diiodobutamidine	C <sub>4</sub> H <sub>8</sub>	I	I	

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TABLE I (continued)

AROMATIC DIAMIDINES

5	Drug Name	R <sub>1</sub> Carbon Chain	R <sub>2</sub>	R <sub>3</sub>	Relative Potency
	Diliodopentamidine	C <sub>5</sub> H <sub>10</sub>	I	I	
10	Diodohexamidine	C <sub>6</sub> H <sub>12</sub>	I	I	
	Dilodoheptamidine	C <sub>7</sub> H <sub>14</sub>	I	I	
	Dilidooctamidine	C <sub>8</sub> H <sub>16</sub>	I	I	
15	Dilidononamidine	C <sub>9</sub> H <sub>18</sub>	I	I	
	Monochloromonobromopropamidine	C <sub>3</sub> H <sub>6</sub>	Cl	Br	
20	Monochloromonobromobutamidine	C <sub>4</sub> H <sub>8</sub>	Cl	Br	
25	Monochloromonobromopentamidine	C <sub>5</sub> H <sub>10</sub>	Cl	Br	
	Monochloromonobromohexamidine	C <sub>6</sub> H <sub>12</sub>	Cl	Br	
30	Monochloromonobromoheptamidine	C <sub>7</sub> H <sub>14</sub>	Cl	Br	
	Monochloromonobromooctamidine	C <sub>8</sub> H <sub>16</sub>	Cl	Br	
35	Monochloromonobromononamidine	C <sub>9</sub> H <sub>18</sub>	Cl	Br	
40	Monochloromonoiodopropamidine	C <sub>3</sub> H <sub>6</sub>	Cl	I	
	Monochloromonoiodobutamidine	C <sub>4</sub> H <sub>8</sub>	Cl	I	
45	Monochloromonoiodopentamidine	C <sub>5</sub> H <sub>10</sub>	Cl	I	
	Monochloromonoiodohexamidine	C <sub>6</sub> H <sub>12</sub>	Cl	I	
50	Monochloromonoiodoheptamidine	C <sub>7</sub> H <sub>14</sub>	Cl	I	
	Monochloromonoiodooctamidine	C <sub>8</sub> H <sub>16</sub>	Cl	I	
55	Monochloromonoiodononamidine	C <sub>9</sub> H <sub>18</sub>	Cl	I	
60	Monobromomonoiodopropamidine	C <sub>3</sub> H <sub>6</sub>	Br	I	
	Monobromomonoiodobutamidine	C <sub>4</sub> H <sub>8</sub>	Br	I	
65					

TABLE I (continued)

## AROMATIC DIAMIDINES

5	Drug Name	R <sub>1</sub> Carbon Chain	R <sub>2</sub>	R <sub>3</sub>	Relative Potency
	Monobromomonoiodo-				
	pentamidine	C <sub>5</sub> H <sub>10</sub>	Br	I	
10	Monobromomonoiodo-				
	hexamidine	C <sub>6</sub> H <sub>12</sub>	Br	I	
15	Monobromomonoiodo-				
	heptamidine	C <sub>7</sub> H <sub>14</sub>	Br	I	
	Monobromomonoiodo-				
	octamidine	C <sub>8</sub> H <sub>16</sub>	Br	I	
20	Monobromomonoiodo-				
	nonamidine	C <sub>9</sub> H <sub>18</sub>	Br	I	

In addition to the specified aromatic diamidines listed in Table I, other aromatic diamidines, aromatic monomidines and non-aromatic diamidines may also be utilized in accordance with the principles of the present invention.

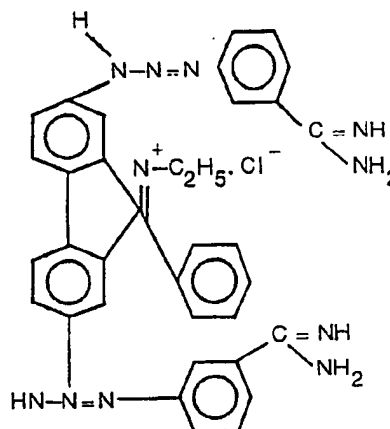
Further, in addition to the aromatic diguanidines, which, as noted above, are similar to the aromatic diamidines listed in Table I except for the substitution of the guanidine group for the amidine group in the drug and which, when trivial names have been assigned thereto will have trivial names similar to those shown in Table I other aromatic diguanidines, aromatic monoguanidines, non-aromatic monoguanidines and non-aromatic diguanidines may also be utilized in accordance with the principles of the present invention.

Further, it has been found that the following compounds are also useful in the practice of the present invention:

## 35 DRUG

## SPECIFIC FORMULA

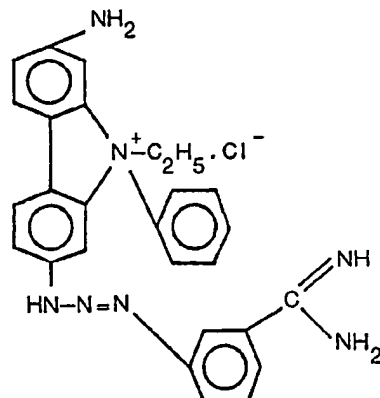
3,8-Di(*m*-aminophenyldiazoamino-  
5-ethyl-6-phenylphenanthridinium  
chloride dihydrochloride hydrate  
(aromatic diamidine)



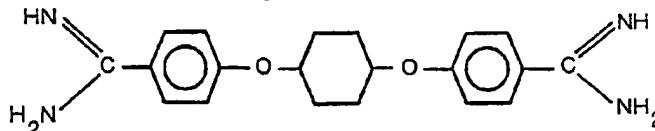
## DRUG

## SPECIFIC FORMULA

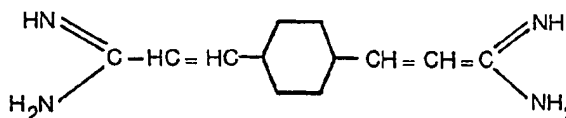
8-(m-amidophenyldiazoamino)-3-amino-5-ethyl-6-phenylphenanthridinium chloride  
(aromatic monoamidine)



1,4-di (p-amidinophenoxy) cyclohexane  
(aromatic diamidine)



1,4-di (2-amidinovinyl) cyclohexane  
(nonaromatic diamidine)



The relative potency shown in Table 1 is expressed in relationship to dibromopropamidine, which has been discovered to be a highly potent fibrinolytic inhibitor. The numerical values are expressed as a reciprocal of the concentration of the drug producing the equivalent inhibition to the dibromopropamidine. Where no values for relative potency are listed such values have not been specifically determined.

The exact relative potency for the guanidines of the present invention has not yet been completely determined. However those skilled in the art may rapidly determine the relative potency for any particular guanidine selected.

Referring now to the drawing, there are illustrated in Figs. 1 through 5 thereof various forms of IUDs useful in the practice of the present invention. According to the principles of the present invention many of the forms shown in Figs. 1 through 5, as well as many other geometrical configurations of IUDs may be utilized in the practice of the present invention. Thus, the illustration of the IUDs illustrated in Figs. 1 through 5 herein is not limiting to the principles of the practice of the present invention.

In the embodiment 10 of the intrauterine device shown in Fig. 1 it is generally comprised of a body member 12 having first walls 14 defining a fluid receiving cavity 16. In the embodiment 10 the first walls 14 are of a semi-flexible nature and are fabricated of, for example, the polymer of:

1. low density polyethylene, or,
2. polyethyl vinyl acetate.

In the embodiment 10, as can be seen, the cavity 16 is substantially coextensive with the first walls 14.

Contained within the cavity 16 is a concentrated fluid solution of the drug. The drug may be in a concentrated aqueous or organic or non-organic hydrophobic solution 18 within the cavity 16. The solution would be in a concentration range from 50 to 200 milligrams per milliliter or approximately 5 to 25% by weight. Additionally, the drug may also be provided in the form of a suspension.

Specifically, in the embodiment 10 shown in Fig. 1, wherein the wall 14 of the body member are semi-flexible, the drug could be provided in a crystalline form in the cavity 16 either with or without a solvent and in the range of 10 to 50% by weight. Further, instead of the crystalline form of the drug, the drug may consist of a concentrated paste with a minimal amount of solvent sufficient to provide the desired viscosity and/or consistency and providing the above-described concentration level. With the wall 14 of the body member 12 fabricated from the above-mentioned materials, the walls 14 are permeable to the drug contained within the cavity 16.

Fig. 1A illustrates another embodiment of the present invention generally designated 10' which is generally similar to the embodiment 10 of Fig. 1. However, in the embodiment 10', the cavity 16 is not coextensive with the first walls 14 but only extends in the region defined by the walls 14a. The walls 14' define the remainder of the body member 12 and no cavity is provided in this area. The concentrated fluid solution of the drug 18 is contained only within the cavity 16.

It will be appreciated, of course, that as utilized herein the term "concentrated fluid solution of the drug" also defines a concentrated fluid suspension of the drug.

In another embodiment of the present invention generally designated 20 as shown in Fig. 2, the IUD generally designated 12 having first walls 20 defining a cavity 16 in the upper portion 12a of the IUD 12. The first walls 20 are flexible walls and the upper portion 20a, in application, may be inserted into the uterus with the lower portion 12b of the body member 12 extending through the uterus, e.g., through the uterine cervical canal, the regions external to the uterus, e.g., the vagina. When inserted, the first walls 20 are collapsed so that it may be passed through the cervical canal into the uterine cavity. After insertion into the uterine cavity the cavity of the device 16 may be filled, thereby inflating the first wall 20 and cavity 16, and the device is thus filled with a concentrated solution of the drug generally designated 18. In this, and in the embodiments 30, 40 and 50 shown, respectively, in Figs. 3, 4 and 5, the drug is provided in the form of the concentrated solution described above in connection with the embodiment 10 shown in Fig. 1. After the cavity 16 has been filled to the desired volume with the concentrated solution of the drug, the portion 12b of the body member 12 extending external to the uterus may be suitably sealed, for example, by tying a knot therein and the IUD left in place in the uterus for the desired time period. The embodiments 30, 40 and 50 shown in Figs. 3, 4 and 5, respectively, are generally similar to the embodiment 20 shown in Fig. 2 except that the shape of the upper portion 12a of the body member 12 is provided in different shapes or configurations. That is, in embodiment 30 of Fig. 3 the upper portion 12a is in the form of a "top" in the embodiment 40 of Fig. 4 the upper portion 12a is in a spherical form. In the embodiment 50 of Fig. 5 the upper portion 12a is in an ovoid form. It will be appreciated that many other shapes may be provided for the upper portion 12a.

In the IUDs shown in Figs. 1 through 5, the drug may, in addition to being provided in the cavity 16, also be provided in the walls 14 of Fig. 10 or walls 20 of Figs. 2 through 5. Accordingly, the drug may be in a simple mixture with the polymer matrix defining the walls 14 or 20. The shape, charge, and other characteristics of the drug molecule such as its hydrophobicity, as well as similar characteristics of the polymer matrix of the walls 14 and 20 may be varied as desired to select the particular release rate of the drug from the walls of 14 and 20 to provide the desired total release rate of the drug into the intrauterine cavity when considering the release rate of the drug from the solution 18.

The ratio of the mixture of the drug contained within the walls 14 or 20 may be on the order of, for example, 10% to 50% by weight depending upon the potency of the drug and the particular polymer matrix from which the body member 12 is fabricated.

The drug may also be provided as a biodegradable polymer or copolymer and mixed into the walls 14 and 20 with selections of characteristics and ratios of weight as above defined.

The drug may also be provided in the biodegradable polymer or copolymer form and covalently bonded with the polymer matrix of the walls 14 or 20 of the body member 12 either within the walls or on the surface thereof.

Further, a biodegradable cross-linked polymer or copolymer coating of the drug bonded covalently to the outer surface 14a or 20a of the body member 12 to provide a soft hydrogel coating thereover. Such a coating is likely to be particularly effective in aiding retention of the IUD in the uterus during the time period soon after insertion thereof. The coating may be provided over all or part of the external surface 14a or 20a. The characteristics of the coating may be selected to provide the desired release rate of the drug into the uterine cavity when considered with the release of the drug from the solution 18 described above, or may be selected to provide specific additional release rates in certain portions thereof such as those in contact with the walls of the uterus.

Further, the drug may also be provided in a non-biodegradable monomer, dimer or oligomer or a cross-linked polymer on the outer surface 14a or 20a of the body member 12. This coating may be provided by covalent or other chemical bonding between the drug molecules and the outer surface 14a or 20a. Since the bleeding of the endometrium is at the interface between the endometrium and the IUD, the solid phase and enzyme inhibition provided by the drug at the point of contact between the endometrium and the IUD can reduce the bleeding associated with utilization of an IUD.

Further, since, as noted above, copper release has also proven anti-conceptive in IUDs, a portion of the outer surface 14a or 20a may be provided with a coating of metallic copper such as a thin wire, copper plating, or the like.

It has been found that the drugs according to the present invention, quite unexpectedly provide an anti-conceptive effect. It is believed that this effect, which should enhance the anti-conceptive effect of the intrauterine device itself, is due to the activity of the drug and its action on the very early embryo and possibly on the sperm.

Further, it is believed yet an additional unexpected and surprising result may be obtained due to the anti-proteolytic action of the drug. This effect is a reduction in the pain and/or cramps and expulsion heretofore associated with utilization of intrauterine devices including medicated IUDs.

The range of concentrations necessary to provide the desired effects mentioned above depend, of course, upon the particular drug or combinations selected. For example, for dipromopropamidine introduced into the uterine cavity and endometrial tissue water, and with an endometrial water turnover rate of 200 milliliters per day and with complete distribution of the drug in the endometrial water turned over, an intrauterine release rate of 50 to 200  $\mu\text{g}$  per day would be expected to produce a concentration of dipromopropamidine in the range of  $0.5$  to  $2.0 \times 10^{-6}$  moles per litre in endometrial water. Since, in general, there will be less than complete distribution of the drug into the endometrial water turned over each day, the concentration of the drug in the uterine cavity could reach much higher levels; for example, on the order of  $10^{-6}$  to  $10^{-4}$  moles per litre. This concentration range is sufficient to provide both the anti-fibrinolytic effects as well as the anti-conceptive or anti-fertility effects desired, and also, it is believed, the reduction in pain, cramps and expulsion. With the above release rate (50—200 mcg per day) and the known sizes of intrauterine devices currently available, and the amount of drug which can be incorporated into such devices, an effective life span of, for example, at least one to three years can be provided for such medicated devices.

The concentration of the drug in the solution, which may be a concentrated aqueous or organic or non-organic hydrophobic solution contained within the cavity of an inflatable IUD would range from 50 mg, or less, to 200 mg per ml (5% to 20% by weight). As noted, this may be a solution or suspension. The concentration required in a hollow core device would range from about 10%, or less, to about 50% by weight and would consist of the crystalline form of the drug packed into the hollow core without solvent, or consist of a highly concentrated paste of the drug with minimal solvent.

At least one aromatic guanidine, NPGb as identified above, has an anti-fibrinolytic effect on the order of 100 times greater than that of dibromopropamidine (on a molar concentration basis). As little as 0.5 to 2.0  $\mu\text{g}$  per day release of NPGb from a medicated IUD according to the principles of the present invention may be satisfactorily effective. Thus, the estimated range of daily release of the drug according to the present invention from a medicated IUD may be as low as, for example, 0.5 mcg to as high as 200  $\mu\text{g}$ , depending upon the particular constituents selected for inclusion in the drug. The useful life span of a device releasing, for example, 0.5  $\mu\text{g}$  per day may greatly exceed three years.

Those skilled in the art, of course, can readily determine the appropriate release rate desired for any drug or combination thereof which may be utilized according to the present invention and, in accordance with known principles, establish the desired release rate thereof to achieve effectiveness.

Medicated intrauterine devices wherein the medicament is a guanidine or amidine are described and claimed in my copending European Patent Application No. 80300257 (EP—A—24779).

#### Claims

1. A medicated intrauterine device of the type insertable in the uterus and having a surface adapted to contact the uterus and said device including at least one wall defining a fluid-receiving cavity for a medicament said wall serving to control the rate of release of the medicament characterised in that the medicament is a drug comprising an amidine and/or a guanidine or an ester or salt thereof which is capable of exhibiting an anti-proteolytic, an anti-fibrinolytic and anti-conceptive effect when released at said controlled rate.

2. The device defined in Claim 1 wherein the controlled rate is 50 to 200  $\mu\text{g}$  per day.

3. The device defined in Claim 1 wherein:  
said first walls are semi-flexible.

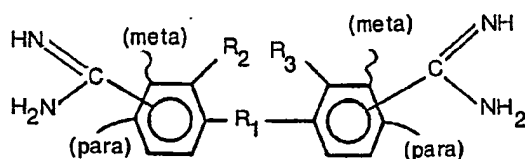
4. The device defined in Claim 1, 2 or 3 wherein:  
said first walls define an inflatable cavity.

5. The device defined in any one of Claims 1 to 4 wherein said at least one drug is:

- (a) an amidine;
- (b) a mixture of an amidine and a guanidine;
- (c) a mixture of more than one amidine and a guanidine;
- (d) a mixture of an amidine and more than one guanidine;
- (e) a mixture of more than one amidine and more than one guanidine;
- (f) a guanidine; and
- (g) a mixture of more than one guanidine.

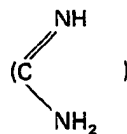
6. The device defined in any one of the preceding claims in which the amidine is an aromatic monoamidine, aromatic diamidine or a non-aromatic diamidine.

7. The device defined in any one of the preceding claims wherein:  
said drug is selected from the class consisting of aromatic diamidines of the group



in which each amidine group

5



10

may be substituted in either a meta or para position with respect to R<sub>1</sub>

R<sub>1</sub> is selected from the group consisting of C<sub>6</sub>H<sub>5</sub>; and

R<sub>2</sub> and R<sub>3</sub> are selected from the group consisting of hydrogen, chlorine, bromine, iodine, hydroxyl group and alkyl groups; and

15



represents the benzene ring.

20

8. The device defined in any one of Claims 1 to 5 wherein:

said drug is selected from the class consisting of: 3,8-Di(*m*-amidinophenyldiazoamino)-5-ethyl-6-phenylphenanthridinium chloride dihydrochloride hydrate 8-*m*(*m*-Amiophenyldiazoamino-3-amino-5-ethyl-6-phenylphenanthridinium chloride,

1,4-di (*p*-amidinophenoxy) cyclohexane, and

1,4-di (2 amidinovinyl) cyclohexane.

25

9. The device defined in any of claims 1 to 5 wherein:

said guanidine of said at least one drug is selected from the class consisting of:

(a) aromatic monoguanidines;

(b) aromatic diguanidines;

(c) non-aromatic monoguanidines; and

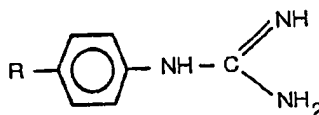
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(d) non-aromatic diguanidines.

10. The device defined in any one of Claims 1 to 5 wherein:

at least one drug is selected from the class of aromatic monoguanidines of the group:

35



wherein R is selected from the class consisting of:

40

(a) a carbon chain free of other elements;

(b) a carbon chain with at least one other element;

(c) an aromatic group free of additional carbon atoms, carbon chains and other elements;

(d) an aromatic group with at least one addition selected from the class consisting of carbon atoms, carbon chains and other elements;

45

(e) a cyclic non-aromatic group free of additional carbon atoms, carbon chains and other elements;

(f) a cyclic non-aromatic group with at least one addition selected from the class consisting of carbon atoms, carbon chains, and other elements; and

(g) a combination of at least two of (a), (b), (c), (d), (e) and (f); and

50

wherein:

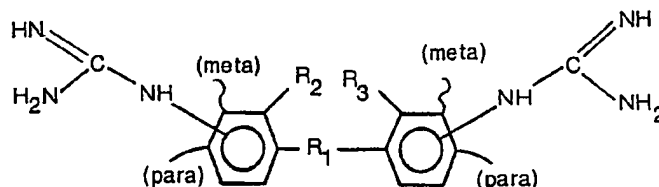


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represents the benzene ring; and/or

at least one drug is selected from the class of aromatic diguanidines of the group:

60



65

and wherein each guanidine group



is in one of a meta or para position with respect to R<sub>1</sub>, and in which:

10 R<sub>1</sub> is selected from the class consisting of:

(a) a hydrocarbon chain free of ether and ester bonds to the benzene ring; and

(b) a hydrocarbon chain having at least one bond selected from the class of ether bonds and ester bonds to the benzene ring;

R<sub>2</sub> and R<sub>3</sub> are selected from the class consisting of:

15 hydrogen, chlorine, bromine, iodine, hydroxyl group and alkyl group; and



20 represents the benzene ring; and/or at least one drug is selected from the class of non-aromatic monoguanidines of the group:



30 wherein R is selected from the class consisting of:

(a) a carbon chain free of other elements;

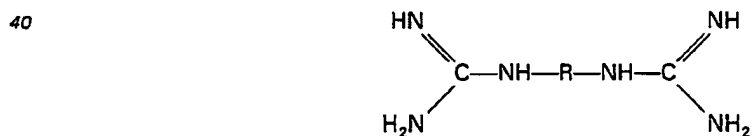
(b) a carbon chain with at least one other element;

(c) a cyclic non-aromatic group free of additional carbon atoms, carbon chains and other elements;

35 (d) a cyclic non-aromatic group with at least one addition selected from the class consisting of carbon atoms, carbon chains and other elements;

(e) a combination of at least two of (a), (b), (c), and (d); and/or

at least one drug is selected from the class consisting of non-aromatic diguanidines of the group:



45 wherein R is selected from the class consisting of:

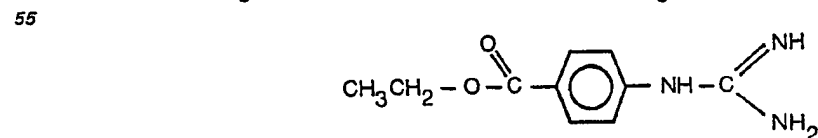
(a) a carbon chain free of other elements;

(b) a carbon chain with at least one other element;

(c) a cyclic non-aromatic group free of additional carbon atoms, carbon chains and other elements;

50 (d) a cyclic non-aromatic group with at least one addition selected from the class consisting of carbon atoms, carbon chains and other elements;

(e) a combination of at least two of (a), (b), (c), and (d); and/or  
at least one drug is selected from the class consisting of:

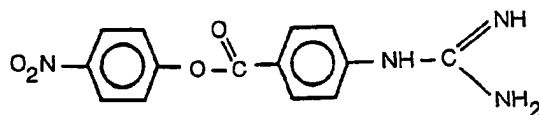


60 ethyl-p-guanidinobenzoate,

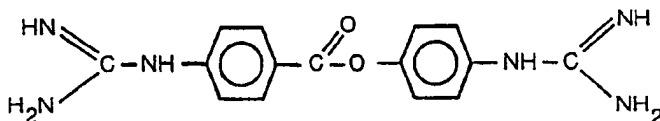
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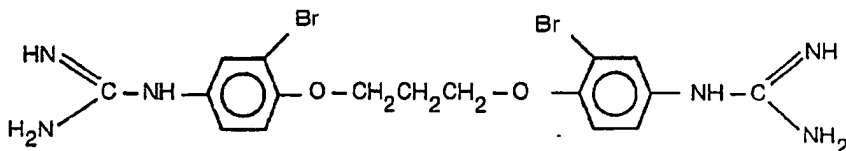
0 024 780



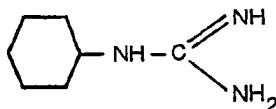
p-nitrophenyl-p'-guanidinobenzoate (commonly named NPGB),



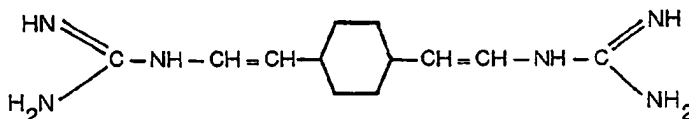
p-guanidinophenyl-p'-guanidinobenzoate,



1,3-bis (2-bromo-4-guanidinophenoxy) propane,



guanidinocyclohexane, and



1,4-di(2-guanidinovinyl)cyclohexane.

11. The device defined in any one of the preceding claims and further comprising:  
a coating on at least a portion of said surface of said intrauterine device, and said coating comprising one of a biodegradable cross-linked polymer and co-polymer of a drug selected from the same group as said drug in said cavity.

12. The device defined in any one of the preceding claims and further comprising: a coating on at least some of said surfaces of said intrauterine device, and said coating comprising one of a non-biodegradable monomer, dimer, oligomer and cross-linked polymer of a drug selected from the same group as said drug in said cavity.

13. The device defined in any one of the preceding claims and further comprising: a coating of copper on a portion of the surface of said body member.

14. The device defined in any one of the preceding claims and further comprising: a coating on at least a first portion of said surface of said intrauterine device, and said coating comprising one of a biodegradable cross-linked polymer and co-polymer of a second drug, and said second drug comprises at least a guanidine, and said second drug being chemically bonded to said first portion of said surface.

15. The device defined in any one of claims 1 to 13 and further comprising: a coating on at least a first portion of said surface of said intrauterine device, and said coating comprising one of a non-biodegradable monomer, dimer, oligomer and cross-linked polymer of a second drug, and said second drug comprises at least a guanidine.

16. The device defined in Claim 14 or Claim 15 wherein: said second drug is selected from the class consisting of:

- (a) a mixture of an amidine and a guanidine;
- (b) a mixture of more than one amidine and a guanidine;
- (c) a mixture of an amidine and more than one guanidine;
- (d) a mixture of more than one amidine and more than one guanidine;
- (e) a guanidine; and
- (f) a mixture of more than one guanidine.

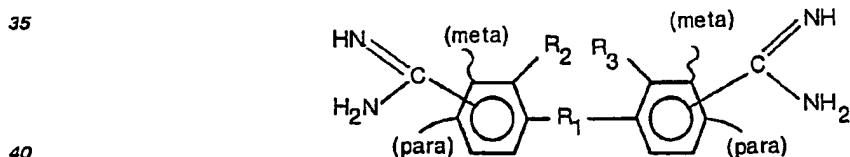
17. The device defined in Claim 14 or Claim 15 wherein: said guanidine of said second drug is selected from the class consisting of:

- (a) aromatic monoguanidines;
- (b) aromatic diguanidines;
- (c) non-aromatic monoguanidines; and
- (d) non-aromatic diguanidines.

5 18. A device according to any of Claims 1 to 17 in which the drug in said cavity is in a solution, suspension, paste or crystalline form.

# Patentansprüche

- 10 1. Medikamenthaltige intrauterine Vorrichtung der In den Uterus einführbaren Art, mit einer zur Berührung mit dem Uterus bestimmten Fläche und mit mindestens einer Wand, die einen flüssigkeitsaufnehmenden Hohlraum für ein Medikament begrenzt und zur Steuerung der Abgabegeschwindigkeit des Medikaments dient, dadurch gekennzeichnet, dass als Medikament ein Arzneimittel vorliegt, das aus einem Amidin und/oder einem Guanidin bzw. einem Ester oder Salz davon besteht, das bei
- 15 Abgabe mit der besagten gesteuerten Geschwindigkeit eine antiproteolytische, antifibrinolytische und empfängnisverhütende Wirkung ausüben kann.
- 2. Vorrichtung nach Anspruch 1, worin die gesteuerte Geschwindigkeit 50 bis 200  $\mu\text{g}$  pro Tag beträgt.
- 3. Vorrichtung nach Anspruch 1, worin diese ersten Wände halbbiegsam sind.
- 20 4. Vorrichtung nach Anspruch 1, 2 oder 3, worin diese ersten Wände einen dehnbaren Hohlraum begrenzen.
- 5. Vorrichtung nach einem der Ansprüche 1 bis 4, worin dieses mindestens eine Arzneimittel
- (a) ein Amidin,
- (b) ein Gemisch aus einem Amidin und einem Guanidin,
- 25 (c) ein Gemisch aus mehr als einem Amidin und einem Guanidin,
- (d) ein Gemisch aus einem Amidin und mehr als einem Guanidin,
- (e) ein Gemisch aus mehr als einem Amidin und mehr als einem Guanidin,
- (f) ein Guanidin oder
- (g) ein Gemisch aus mehr als einem Guanidin darstellt.
- 30 6. Vorrichtung nach einem der vorhergehenden Ansprüche, worin als Amidin ein aromatisches Monoamidin, aromatisches Diamidin oder nicht-aromatisches Diamidin vorliegt.
- 7. Vorrichtung nach einem der vorhergehenden Ansprüche, worin dieses Arzneimittel aus der aromatischen Diamidine der Gruppe



worin jede substituierende AmidinGruppe



- 50 entweder in meta- oder para-Stellung zu  $R_1$  stehen kann,  $R_1$  aus der  $C_6H_5$  darstellenden Gruppe ausgewählt ist sowie  $R_2$  und  $R_3$  aus der Wasserstoff, Chlor, Brom, Jod, den Hydroxylrest und Alkylreste umfassenden Gruppe ausgewählt sind und

55

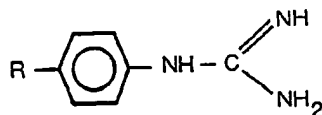


den Benzolring darstellt, umfassenden Klasse ausgewählt ist.

- 60 8. Vorrichtung nach einem der Ansprüche 1 bis 5, worin dieses Arzneimittel aus der 3,8-Di-(m-amidinophenyldiazoamino)-5-äthyl-6-phenylphenanthridiniumchlorid-dihydrochloridhydrat, 8-m-(m-Amidinophenyldiazoamino)-3-amino-5-äthyl-6-phenylphenanthridiniumchlorid, 1,4-Di-(p-amidinophenoxy)-cyclohexan und 1,4-Di-(2-amidinovinyl)-cyclohexan umfassenden Klasse ausgewählt ist.
- 9. Vorrichtung nach einem der Ansprüche 1 bis 5, worin dieses Guanidin in dem besagten mindestens einem Arzneimittel aus der
- 65 (a) aromatische Monoguanidine,

- (b) aromatische Diguanidine,  
 (c) nicht-aromatische Monoguanidine und  
 (d) nicht-aromatische Diguanidine umfassenden Klasse ausgewählt ist.

10. Vorrichtung nach einem der Ansprüche 1 bis 5, worin mindestens ein Arzneimittel aus der  
 5 aromatische Monoguanidine der Gruppe

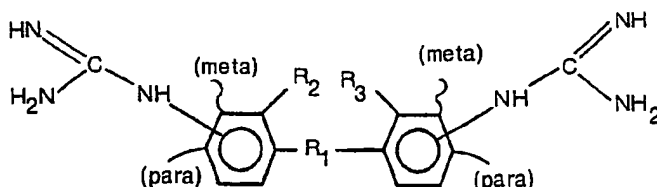


worin R aus der

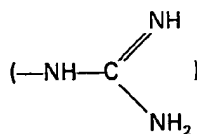
- (a) eine von weiteren Elementen freie Kohlenstoffkette,  
 (b) eine Kohlenstoffkette mit mindestens einem weiteren Element,  
 15 (c) eine von zusätzlichen Kohlenstoffatomen, Kohlenstoffketten und weiteren Elementen freie aromatische Gruppe,  
 (d) eine aromatische Gruppe mit mindestens einem aus der Kohlenstoffatome, Kohlenstoffketten und weitere Elemente umfassenden Klasse ausgewählten Zusatz,  
 (e) eine von zusätzlichen Kohlenstoffatomen, Kohlenstoffketten und weiteren Elementen freie cyclische nicht-aromatische Gruppe,  
 20 (f) eine cyclische nicht-aromatische Gruppe mit mindestens einem aus der Kohlenstoffatome, Kohlenstoffketten und weitere Elemente umfassenden Klasse ausgewählten Zusatz und  
 (g) eine Kombination von mindestens zwei unter (a), (b), (c), (d), (e) und (f) umfassenden Klasse ausgewählt ist und



30 den Benzolring darstellt, umfassenden Klasse ausgewählt ist und/oder mindestens ein Arzneimittel aus der aromatische Diguanidine der Gruppe



40 worin sich jede Guanidingruppe



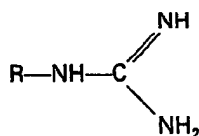
in einer der meta- oder para-Stellungen zu R<sub>1</sub> befindet und R<sub>1</sub> aus der

- 50 (a) eine von Aether- und Esterbindungen an den Benzolring freie Kohlenwasserstoffkette und  
 (b) eine Kohlenwasserstoffkette mit mindestens einer Aetherbindungen und Esterbindungen an den Benzolring umfassenden Gruppe ausgewählten Bindung umfassenden Klasse ausgewählt ist,  
 R<sub>2</sub> und R<sub>3</sub> aus der Wasserstoff, Chlor, Brom, Jod, die Hydroxylgruppe und Alkylgruppen umfassenden Klasse ausgewählt sind und



60 den Benzolring darstellt, umfassenden Klasse ausgewählt ist und/oder mindestens ein Arzneimittel aus der nicht-aromatische Monoguanidine der Gruppe

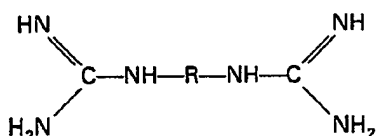
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5

worin R aus der aus

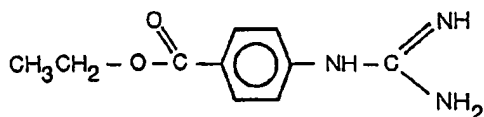
- (a) einer von weiteren Elementen freien Kohlenstoffkette,  
 (b) einer Kohlenstoffkette mit mindestens einem weiteren Element,  
 10 (c) einer von zusätzlichen Kohlenstoffatomen, Kohlenstoffketten und weiteren Elementen freien cyclischen nicht-aromatischen Gruppe,  
 (d) einer cyclischen nicht-aromatischen Gruppe mit mindestens einem aus der Kohlenstoffatome, Kohlenstoffketten und weitere Elemente umfassenden Klasse ausgewählten Zusatz,  
 (e) einer Kombination von mindestens zwei unter (a), (b), (c) und (d) bestehenden Gruppe ausge-  
 15 wählt ist umfassenden Klasse ausgewählt ist und/oder mindestens ein Arzneimittel aus der nicht-aromatische Diguanidine der Gruppe



20

worin R aus der aus

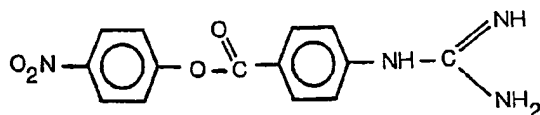
- (a) einer von weiteren Elementen freien Kohlenstoffkette,  
 25 (b) einer Kohlenstoffkette mit mindestens einem weiteren Element,  
 (c) einer von zusätzlichen Kohlenstoffatomen, Kohlenstoffketten und weiteren Elementen freien cyclischen nicht-aromatischen Gruppe,  
 (d) einer cyclischen nicht-aromatischen Gruppe mit mindestens einem aus der Kohlenstoffatome, Kohlenstoffketten und weitere Elemente umfassenden Klasse ausgewählten Zusatz,  
 30 (e) einer Kombination von mindestens zwei unter (a), (b), (c) und (d) bestehenden Gruppe ausgewählt ist, umfassenden Klasse ausgewählt ist und/oder mindestens ein Arzneimittel aus der



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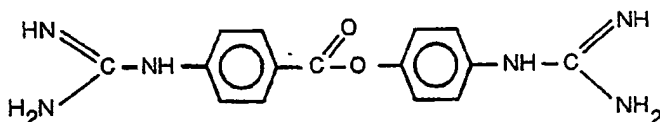
Aethyl-p-guanidinobenzoat,

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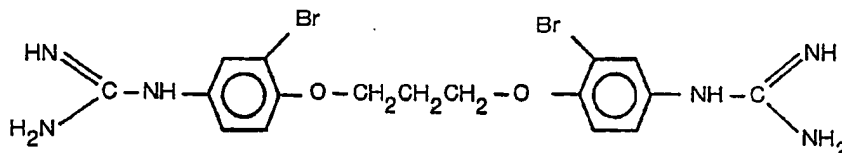
p-Nitrophenyl-p'-guanidinobenzoat (allgemein als NPGB bezeichnet),



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p-Guanidinophenyl-p'-guanidinobenzoat,

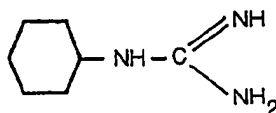
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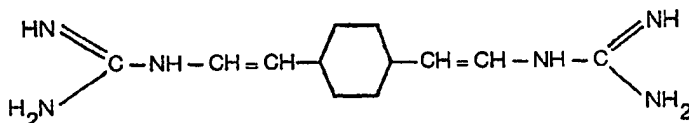
60

1,3-Bis-(2-brom-4-guanidinophenoxy)-propan,

65



Guanidinocyclohexan und



1,4-Di-(2-guanidinovinyl)-cyclohexan umfassenden Klasse ausgewählt ist.

11. Vorrichtung nach einem der vorhergehenden Ansprüche, welche ferner auf mindestens einem Teil jener Fläche der besagten intrauterinen Vorrichtung einen Ueberzug aufweist, der ein biologisch abbaubares vernetztes Polymer oder Copolymer eines aus derselben Gruppe wie dieses Arzneimittel in jenem Hohlraum ausgewählten Arzneimittels enthält.

12. Vorrichtung nach einem der vorhergehenden Ansprüche, welche ferner auf mindestens einigen jener Flächen der besagten intrauterinen Vorrichtung einen Ueberzug aufweist, der ein biologisch nicht-abbaubares Monomer, Dimer, Oligomer oder vernetztes Polymer eines aus derselben Gruppe wie dieses Arzneimittel in jenem Hohlraum ausgewählten Arzneimittels enthält.

13. Vorrichtung nach einem der vorhergehenden Ansprüche, welche ferner auf einem Teil der Fläche des besagten Körperglieds (?) einen Kupferüberzug aufweist.

14. Vorrichtung nach einem der vorhergehenden Ansprüche, welche ferner auf mindestens einem ersten Teil jener Fläche der besagten intrauterinen Vorrichtung einen Ueberzug aufweist, der ein biologisch abbaubares vernetztes Polymer oder Copolymer eines zweiten Arzneimittels enthält, das aus mindestens einem Guanidin besteht und chemisch an jenen ersten Teil der besagten Fläche gebunden ist.

15. Vorrichtung nach einem der Ansprüche 1 bis 13, welche ferner auf mindestens einem ersten Teil jener Fläche der besagten intrauterinen Vorrichtung einen Ueberzug aufweist, der ein biologisch nicht-abbaubares Monomer, Dimer, Oligomer oder vernetztes Polymer eines zweiten Arzneimittels enthält, das aus mindestens einem Guanidin besteht.

16. Vorrichtung nach Anspruch 14 oder 15, worin dieses zweite Arzneimittel aus der

- (a) ein Gemisch aus einem Amidin und einem Guanidin,
- (b) ein Gemisch aus mehr als einem Amidin und einem Guanidin,
- (c) ein Gemisch aus einem Amidin und mehr als einem Guanidin,
- (d) ein Gemisch aus mehr als einem Amidin und mehr als einem Guanidin,
- (e) ein Guanidin und
- (f) ein Gemisch aus mehr als einem Guanidin umfassenden Klasse ausgewählt ist.

17. Vorrichtung nach Anspruch 14 oder 15, worin dieses Guanidin des besagten zweiten Arzneimittels aus der

- (a) aromatische Monoguanidine,
- (b) aromatische Diguanidine,
- (c) nicht-aromatische Monoguanidine und
- (d) nicht-aromatische Diguanidine umfassenden Klasse ausgewählt ist.

18. Vorrichtung nach einem der Ansprüche 1 bis 17, worin das Arzneimittel in jenem Hohlraum in Form einer Lösung, Suspension oder Paste oder in kristalliner Form vorliegt.

## 50 Revendications

1. Dispositif intra-utérin médicamenteux du type insérable dans l'utérus et ayant une surface adaptée pour faire contact avec l'utérus, ledit dispositif comprenant au moins une paroi définissant une cavité de réception de fluide pour le médicament, ladite paroi servant à contrôler la vitesse de libération du médicament, caractérisé en ce que le médicament est un produit pharmaceutique contenant une amidine et/ou une guanidine, ou un de leurs esters ou sels, qui est capable de présenter un effet anti-protéolytique, anti-fibrinolytique et anti-conceptuel lorsqu'il est libéré à ladite vitesse contrôlée.

2. Dispositif selon la revendication 1, caractérisé en ce que la vitesse contrôlée est de 50 à 200 µg par jour.

3. Dispositif selon la revendication 1, caractérisé en ce que lesdites premières parois sont semi-flexibles.

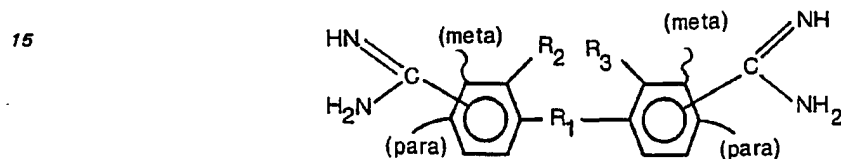
4. Dispositif selon la revendication 1, caractérisé en ce que lesdites premières parois définissent une cavité gonflable.

5. Dispositif selon l'une quelconque des revendications 1 à 4, caractérisé en ce que l'un au moins desdits produits pharmaceutiques est:

- (a) une amidine;  
 (b) un mélange d'une amidine et d'une guanidine;  
 (c) un mélange de plusieurs amidines et d'une guanidine;  
 (d) un mélange d'une amidine et de plusieurs guanidines;  
 (e) un mélange de plusieurs amidines et de plusieurs guanidines;  
 (f) une guanidine; et  
 (g) un mélange de plusieurs guanidines.

6. Dispositif selon l'une quelconque des revendications précédentes, caractérisé en ce que l'amidine est une monoamidine aromatique, une diamidine aromatique ou une diamidine non aromatique.

7. Dispositif selon l'une quelconque des revendications précédentes, caractérisé en ce que: ledit produit pharmaceutique est choisi dans la classe constituée par les diamidines aromatiques du groupe



dans lequel chaque groupe amidine



peut être substitué en position méta ou para par rapport à R<sub>1</sub>;

R<sub>1</sub> est choisi dans le groupe constitué par C<sub>x</sub>H<sub>y</sub>; et

R<sub>2</sub> et R<sub>3</sub> sont choisis dans le groupe constitués par l'hydrogène, le chlore, le brome, l'iode, le groupe hydroxyle et les groupes alkyle; et



représente le noyau benzénique.

8. Dispositif selon l'une quelconque des revendications 1 à 5, caractérisé en ce que: ledit produit pharmaceutique est choisi dans la classe constituée par:

le chlorure de di(*m*-amidinophényldiazoamino)-3,8 éthyl-5 phényl-6 phénanthridinium dichlorohydrate

le chlorure de *m*-(*m*-amidinophényldiazoamino)-8 amino-3 éthyl-5 phényl-6 phénanthridinium,

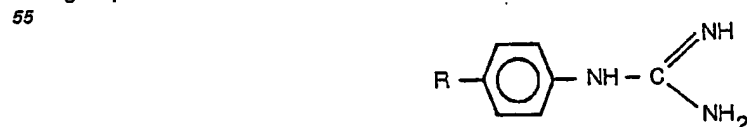
le di *p*-amidinophénoxy)-1,4 cyclohexane, et

le di (amidino-2 vinyl)-1,4 cyclohexane.

9. Dispositif selon l'une quelconque des revendications 1 à 5, caractérisé en ce que: ladite guanidine d'un au moins desdits produits pharmaceutiques est choisie dans la classe constituée par:

- (a) les monoguanidines aromatiques;  
 (b) les diguanidines aromatiques;  
 (c) les monoguanidines non aromatiques; et  
 (d) les diguanidines non aromatiques.

10. Dispositif selon l'une quelconque des revendications 1 à 5, caractérisé en ce que: l'un au moins des produits pharmaceutiques est choisi dans la classe des monoguanidines aromatiques du groupe:



dans lequel R est choisi dans la classe constituée par:

- (a) une chaîne carbonée exempte d'autres éléments;  
 (b) une chaîne carbonée ayant au moins un autre élément;  
 (c) un groupe aromatique exempt d'atomes de carbone, de chaînes carbonées et d'autres éléments supplémentaires;

(d) un groupe aromatique ayant au moins une addition choisie dans la classe constituée par les atomes de carbone, les chaînes carbonées et d'autres éléments;

(e) un groupe cyclique non aromatique exempt d'atomes de carbone, de chaînes carbonées et d'autres éléments supplémentaires;

5 (f) un groupe cyclique non aromatique ayant au moins une addition choisie dans la classe constituée par les atomes de carbone, les chaînes carbonées et d'autres éléments; et

(g) une combinaison d'au moins deux parmi (a), (b), (c), (d), (e) et (f); et dans lequel

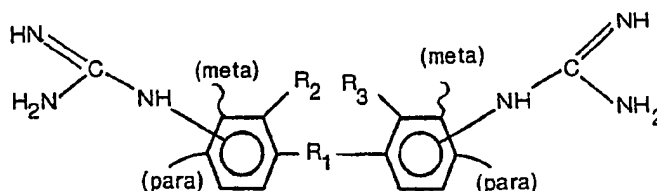
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représente le noyau benzénique; et/ou l'un au moins des produits pharmaceutiques est choisi dans la

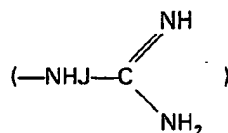
15 classe des diguanidines aromatiques du groupe:

20



25 et dans lequel chaque groupe guanidine

30



est dans l'une des positions méta ou para par rapport à R<sub>1</sub>, et dans lequel:

R<sub>1</sub> est choisi dans la classe constituée par:

35 (a) une chaîne hydrocarbure exempte de liaisons éther et ester sur le noyau benzénique; et  
(b) une chaîne hydrocarbure ayant au moins une liaison choisie dans la classe des liaisons éther et des liaisons ester sur le noyau benzénique;

R<sub>2</sub> et R<sub>3</sub> sont choisis dans la classe constituée par:

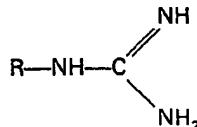
l'hydrogène, le chlore, le brome, l'iode, le groupe hydroxyle et le groupe alkyle; et

40



45 représente le noyau benzénique; et/ou l'un au moins des produits pharmaceutiques est choisi dans la classe des monoguanidines non aromatiques du groupe:

50



dans lequel R est choisi dans la classe constituée par

55 (a) une chaîne carbonée exempte d'autres éléments;  
(b) une chaîne carbonée ayant au moins un autre élément;  
(c) un groupe cyclique non aromatique exempt d'atomes de carbone, de chaînes carbonées et d'autres éléments supplémentaires;

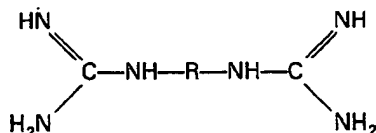
(d) un groupe cyclique non aromatique ayant au moins une addition choisie dans la classe constituée par les atomes de carbone, les chaînes carbonées et d'autres éléments;

60 (e) une combinaison d'au moins deux parmi (a), (b), (c) et (d); et/ou l'un au moins des produits pharmaceutiques est choisi dans la classe constituée par les diguanidines non aromatiques du groupe:

65

0 024 780

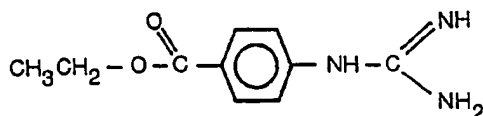
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dans lequel R est choisi dans la classe constituée par:

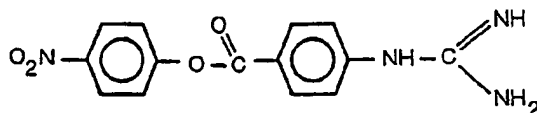
- (a) une chaîne carbonée exempte d'autres éléments;
- (b) une chaîne carbonée ayant au moins un autre élément;
- 10 (c) un groupe cyclique non aromatique exempt d'atomes de carbone, de chaînes carbonées et d'autres éléments supplémentaires;
- (d) un groupe cyclique non aromatique ayant au moins une addition choisie dans la classe constituée par les atomes de carbone, les chaînes carbonées et d'autres éléments;
- (e) une combinaison d'au moins deux parmi (a), (b), (c) et (d); et/ou l'un au moins des produits
- 15 pharmaceutiques est choisi dans la classe constituée par:

20



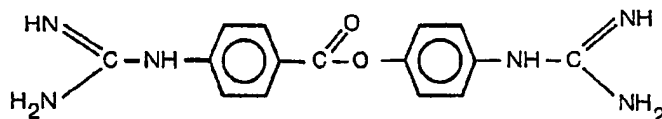
p-guanidinobenzoate d'éthyle,

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p-nitrophényl p'-guanidinobenzoate (appelé couramment NPGB),

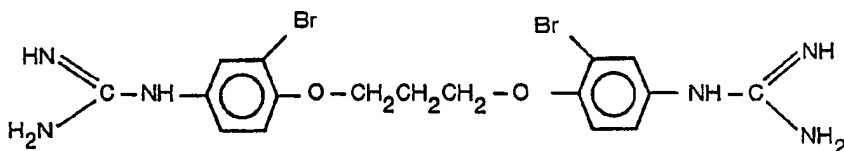
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p-guanidinophényl p'-guanidinobenzoate,

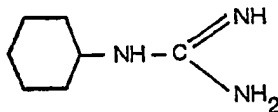
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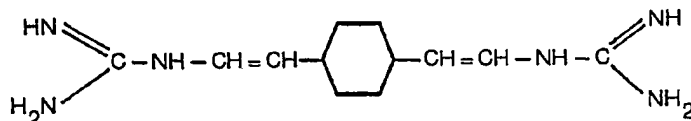
bis (bromo-2 guanidino-4 phénoxy)-1,3 propane,

50



guanidinocyclohexane, et

55



60

di (guanidino-2 vinyl)-1,4 cyclohexane.

11. Dispositif selon l'une quelconque des revendications précédentes, caractérisé en ce qu'il comprend en outre: un enduit sur au moins une partie de la surface dudit dispositif intra-utérin, ledit enduit comprenant l'un parmi un polymère et un copolymère réticulé biodégradable d'un produit

65 pharmaceutique choisi dans le même groupe que ledit produit pharmaceutique le ladite cavité.



12. Dispositif selon l'une quelconque des revendications précédentes, caractérisé en ce qu'il comprend en outre: un enduit sur au moins certaines desdites surfaces dudit dispositif intra-utérin, ledit enduit comprenant l'un parmi un monomère, dimère, oligomère et polymère réticulé non biodégradables d'un produit pharmaceutique choisi dans le même groupe que ledit produit pharmaceutique de ladite cavité.

13. Dispositif selon l'une quelconque des revendications précédentes, caractérisé en ce qu'il comprend en outre: un enduit de cuivre sur une partie de la surface dudit élément de corps.

14. Dispositif selon l'une quelconque des revendications précédentes, caractérisé en ce qu'il comprend en outre: un enduit sur au moins une première partie de ladite surface dudit dispositif intra-utérin, ledit enduit comprenant l'un parmi un polymère et un copolymère réticulé biodégradables d'un second produit pharmaceutique, et ledit second produit pharmaceutique comprend au moins une guanidine, ledit second produit pharmaceutique étant lié chimiquement à ladite première partie de ladite surface.

15. Dispositif selon l'une quelconque des revendications 1 à 13, caractérisé en ce qu'il comprend en outre: un enduit sur au moins une première partie de la dite surface dudit dispositif intra-utérin, ledit enduit comprenant l'un parmi un monomère, un dimère, un oligomère et un polymère réticulé non biodégradables, et le second produit pharmaceutique comprend au moins une guanidine.

16. Dispositif selon la revendication 14 ou 15, caractérisé en ce que: ledit second produit pharmaceutique est choisi dans la classe constituée par:

- (a) un mélange d'une amidine et d'une guanidine;
- (b) un mélange de plusieurs amidines et d'une guanidine;
- (c) un mélange d'une amidine et de plusieurs guanidines;
- (d) un mélange de plusieurs amidines et de plusieurs guanidines;
- (e) une guanidine; et
- (f) un mélange de plusieurs guanidines.

17. Dispositif selon la revendication 14 ou 15, caractérisé en ce que: ladite guanidine dudit second produit pharmaceutique est choisi dans la classe constituée par:

- (a) les monoguanidines aromatiques;
- (b) les diguanidines aromatiques;
- (c) les monoguanidines non aromatiques; et
- (d) les diguanidines non aromatiques.

18. Dispositif selon l'une quelconque des revendications 1 à 17, caractérisé en ce que le produit pharmaceutique de ladite cavité est sous forme de solution, de suspension, de pâte ou cristalline.

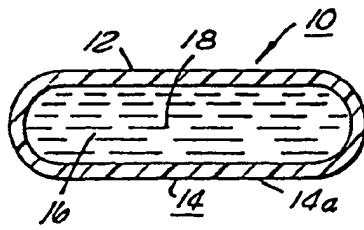


FIG. 1

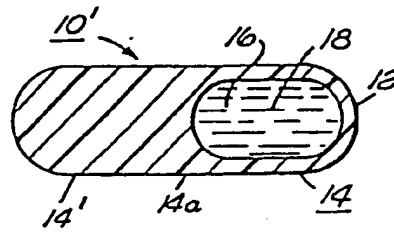


FIG. 1A

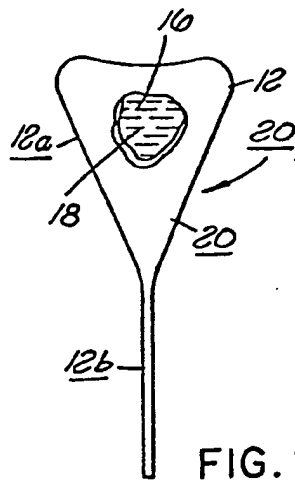


FIG. 2

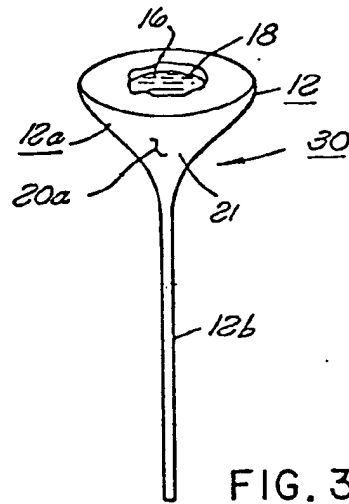


FIG. 3

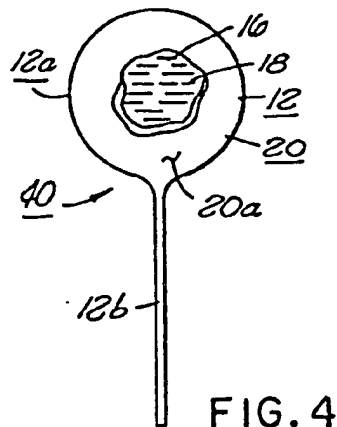


FIG. 4

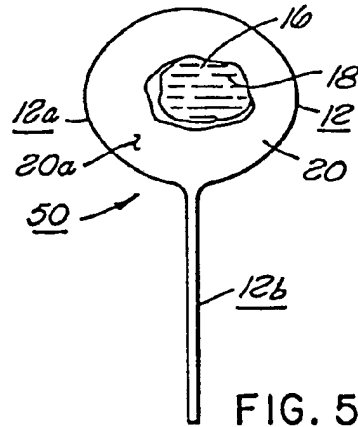


FIG. 5